Remarks/Arguments

I. Claim Amendments

Claims 9 and 15 have been amended to correct typographical errors. Claim 9 has also been amended to correct claim dependency. This Amendment adds no new matter.

II. Rejection of claims 7, 9, 15, 16, 18 and 19 under 35 U.S.C. 103(a) in view of Langer et al.

Claims 7, 9, 15, 16, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Langer et al. (U.S. Pat. No. 6,224,893). The Examiner characterizes Langer et al. as teaching a method of making a semi-interpenetrating network comprising a blend of ionically and covalently crosslinkable polymers, where the covalently crosslinkable polymer is cross-linked. The Examiner relies on Column 10, lines 8-20 of Langer et al. as supporting this contention (Office Action, page 2). The Examiner further states that Langer et al. teaches that the ionically crosslinkable polymer as optionally being hyaluronic acid and the covalently crosslinkable polymer as optionally being chitosan (Office Action, page 2). The Examiner alleges that Langer et al. teaches that the ionic compound is not cross-linked; however, the Examiner does not point to specific language in Langer et al. that provides this teaching (Office Action, pages 2-3). Based on this allegation, the Examiner concludes that the reaction conditions would inherently be such that the amine groups would not be protonated and the hydroxyl groups would not be reacted since this would result in crosslinking of hyaluronic acid. The Examiner admits that Langer et al. does not teach a network specifically comprising the combination of chitosan and an anionic polysaccharide (Office Action, page 3). The Examiner, however, contends that each of these components is described as one of a finite list of possibilities and that it would have been obvious to one of ordinary skill in the art to "choose from a finite list of predictable known options with a reasonable expectation of success" (Office Action, page 3). The Examiner further admits that Langer et al. does not teach the claimed pH range. However, the Examiner contends that Langer et al. does teach that pH affects the degree of crosslinking of ionically crosslinkable polymers. The Examiner contends that it would have been obvious to have optimized the pH through routine optimization. With regard to claims 15 and 16, the Examiner claims that Langer et al. teaches the use of chitosan and that chitosan is by definition, deacetylated

chitin. Regarding claim 19, the Examiner argues that Langer et al. teaches that the network comprises other components of the extracellular matrix.

In Applicant's amendment and response dated January 12, 2009, Applicant presented arguments showing that chitosan is not water soluble. In the current Non-Final Rejection, the Examiner responds by stating that Langer et al. specifically refers to chitosan as being water soluble and that Hudson et al. teaches that chitosan derivatives are water-soluble. The Examiner concludes that it would have been obvious to choose a water-soluble derivative of chitosan for the semi-interpenetrating network. Contrarily, the Examiner then contends that chitosan falls within the definition of a water soluble polysaccharide based on the originally filed claims. The Examiner further contends that the property of chitosan not being soluble at neutral or basic pH is not recited by the claims. In response to Applicant's argument that Langer et al. is only directed to crosslinking hyaluronic acid, the Examiner responds by stating that "Langer et al. is also concerned with semi interpenetrating networks comprising a blend of ionically and covalently crosslinkable polymers where the covalently crosslinkable polymer is crosslinked" (Office Action, page 5).

A. The claimed invention

The instant claims are directed to a method for the preparation of a composition consisting of a semi-interpenetrating network comprising at least one crosslinked water soluble derivative of a basic polysaccharide containing primary and/or secondary amine groups and a non-crosslinked component which comprises at least one anionic polysaccharide, wherein the method comprises crosslinking at least one water-soluble derivative of a basic polysaccharide in the presence of at least one anionic polysaccharide under conditions which avoid protonation of said amine groups and which also avoid reaction of any functional group on the anionic polysaccharide, and wherein the crosslinking reaction is performed at a pH from about 7 to about 8. Claim 15 is directed to the use of a chitosan derivative as the water soluble basic polysaccharide. Claim 18 is directed to the use of hyaluronic acid as the non-crosslinked component.

The claimed method therefore requires:

i. that the crosslinked component be water-soluble;

ii. that the crosslinking reaction be conducted at a pH from about 7 to about 8;

iii. that the crosslinking of the water soluble derivative of a basic polysaccharide be conducted in the presence of the anionic polysaccharide; and

iv. that the anionic polysaccharide is not crosslinked.

B. Langer et al. does not teach a semi-interpenetrating network wherein hyaluronic is not crosslinked

The rejection is based on the Examiner's erroneous characterization that Langer et al. teaches hyaluronic acid as non-crosslinked component of a semi-interpenetrating network. On the contrary, Langer et al. discloses hyaluronic acid as a crosslinked component of the network. As described by Langer et al., semi-interpenetrating networks are solutions that include a crosslinked polymer component and a non-crosslinked polymer component (Column 3, lines 10-13). Langer et al. further teaches two classes of polymers that can be used as the crosslinked polymer component: covalently crosslinkable polymers and ionically crosslinkable polymers. See, for example, Column 2, lines 39-42 which states, "The polymer solutions can be crosslinked ionically or covalently to form a hydrogel, semi-interpenetrating polymer network or an interpenetrating polymer network." The adjective "crosslinkable" indicates that these polymers which are capable of crosslinking can be used as the crosslinked polymer component of the semi-interpenetrating network. The adjective "ionically crosslinkable" thus indicates that the exemplified polymers can be used as a crosslinked component of the interpenetrating or semi-interpenetrating network. Langer et al. describes the non-crosslinked polymer component in the semi-interpenetrating network using the phrase "non-crosslinked polymer" (see, for example, Column 3, line 13; Column 10, line 18), not as "ionically crosslinkable."

Hyaluronic acid is exemplified by Langer et al. as an "ionically crosslinkable and hydrophilic polymer" (Column 3, lines 52 to Column 5, line 2; Column 3, lines 52 to Column 4, line 8). Hyaluronic acid is not described as an example of a non-crosslinked polymer. Hyaluronic acid is only described as an "ionically crosslinkable polymer." The Examiner's rejection therefore ignores the explicit teaching of Langer et al. which characterizes

hyaluronic acid as an example of a crosslinked polymer component of an interpenetrating or semi-interpenetrating network. Langer et al. does not describe any embodiment or teaching where hyaluronic acid is used in an interpenetrating or semi-interpenetrating network as a non-crosslinked polymer.

Furthermore, the Examiner has not pointed to any specific teaching in Langer et al. that supports his very specific contention that Langer et al. teaches the use of hyaluronic acid as a non-crosslinked component of a semi-interpenetrating network. The Examiner relies entirely on Column 10, lines 8-20 of Langer et al. as teaching a method of making a semi-interpenetrating network comprising a blend of ionically and covalently crosslinkable polymers where only the covalently crosslinkable polymer is cross-linked. However, this section of Langer et al. teaches that the blend of ionically and covalently crosslinkable polymers is made of crosslinked ionically crosslinkable polymer and crosslinked covalently crosslinkable polymers. Column 10, lines 8-20 of Langer et al. reads as follows:

> Blends of ionically and covalently crosslinkable polymers
> In a preferred embodiment, the polymer solution is formed of two or more polymers, which crosslink to form a semi-interpenetrating network. For example, the blend could include PEO, which is ionically crosslinkable, and demthacrylated PEO, in a range of 10 and 40% by weight covalently crosslinkable polymer in the preferred embodiment. Alternatively, blends of two covalently crosslinkable polymers can be used, selected on the basis that they form a network of crosslinked homopolymers, not to each other. Advantages of semi-interpenetrating networks include that the diffusion of non-crosslinked polymer can provide advantages degradation properties, and enhance mechanical properties, especially for use in plastic surgery. (emphasis added)

The specific language of Langer et al. states that the term "blends of ionically and covalently crosslinkable polymers" means "a polymer solution is formed of two or more polymers, *which crosslink* to form a semi-interpenetrating network." This language means that both crosslinkable polymers are crosslinked. The Examiner's rejection is based on the mistaken premise that the solution of Langer et al. is formed of two polymers where only one polymer is crosslinked. The explicit language of Langer et al. clearly contradicts this interpretation.

The section of Langer et al. relied upon by the Examiner therefore teaches embodiments where the semi-interpenetrating networks comprises a blend of an ionically crosslinkable polymer and a covalently crosslinkable polymer wherein both crosslinkable polymers are

crosslinked. The semi-interpenetrating network is thus a blend of crosslinked homopolymers. One example of a semi-interpenetrating network described by Langer et al. includes an ionically crosslinkable polymer (PEO) and a covalently crosslinkable polymer (demethacyrlated PEO) which are both crosslinked. Langer et al. does not teach or disclose that the "ionically crosslinkable polymer" is the non-crosslinked polymer in the semi-interpenetrating network.

The Examiner's rejection is therefore based on the erroneous premise that Langer et al. teaches hyaluronic acid as an example of a non-crosslinked polymer component of a semi-interpenetrating network. As discussed above, Langer et al. neither teaches nor suggests that ionically crosslinkable polymers such as hyaluronic acid be used as the non-crosslinked polymer of a semi-interpenetrating network.

C. *Langer et al. does not teach a method of preparing a semi-interpenetrating network comprising a water-soluble derivative of a basic polysaccharide or a crosslinking reaction conducted at neutral or mildly basic pH*

The Examiner contends that Langer et al. teaches that pH affects the degree of crosslinking of ionically crosslinkable polymers (Office Action, page 3). The Examiner opines that it would have been obvious to have optimized the pH and the motivation to do so would have been to reduce the crosslinking of the ionic component. As discussed in detail above, the Examiner has no basis for asserting that Langer et al. teaches or suggests that the ionically crosslinkable polymer be present in a semi-interpenetrating network as a non-crosslinked component. Langer et al. only teaches the use of ionically crosslinkable polymers as part of the crosslinked component. There would therefore be no motivation to modify Langer et al. as asserted by the Examiner.

The teaching relied upon by the Examiner as allegedly teaching that pH affects the degree of crosslinking of ionically crosslinkable polymers is Column 1, lines 27-29. Column 1, lines 23-29 states as follows:

> WO 94/25080 by Massachusetts Institute of Technology describes the use of injectable polysaccharide-cell compositions for delivering isolated cells by injection, which then forms new tissue that is effective as a bulking agent. The polymers that are described crosslink ionically, as a function of ion strength, temperature, pH, or combinations thereof.

This language falls far short of teaching that a crosslinking reaction can be conducted at a pH between about 7 and about 8 such that a water soluble derivative of a basic polysaccharide is crosslinked, but hyaluronic acid, an ionically crosslinkable polymer, is not crosslinked.

Langer et al. provides no guidance as to how water-soluble chitosan derivatives can be crosslinked under the recited reaction conditions. There is no language or working examples directed to crosslinking derivatives of chitosan that would be soluble at the claimed pH ranges. As discussed in detail in Applicant's response dated January 12, 2009, chitosan is not soluble at neutral or mildly basic pH, therefore, the chitosan described by Langer et al. cannot be crosslinked under the claimed reaction conditions. The Examiner contends that the solubility of chitosan derivatives at neutral or basic pH is not recited in the claims (Office Action, pages 4-5). The Examiner is incorrect. The claimed method is directed to the crosslinking of water-soluble chitosan derivatives; that these derivatives are in solution at pH from about 7 to about 8 is an inherent feature of the crosslinking reaction.

Based on the arguments presented above, the Examiner has failed to establish a *prima facie case* of obviousness. Withdrawal of this rejection is therefore respectfully requested.

III. Rejection of claim 17 under 35 U.S.C. 103(a) in view of Langer et al. and further in view of Hudson et al.

Claim 17 is rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Langer et al. in view of Hudson et al. The Examiner contends that Langer et al. teaches that chitosan is soluble in water. The Examiner states that Langer et al. is silent with respect to the acetylation content of chitosan. However, the Examiner alleges that it would have been obvious to have optimized the acetylation content of chitosan and the motivation to do so would have been to obtain a water soluble chitosan for crosslinking (Office Action, page 4). The Examiner relies on Hudson et al. as teaching that the acetylation degree of chitosan is related to its solubility in water.

As discussed above, Langer et al. teaches chitosan as an example of a covalently crosslinkable polymer. Langer et al. does not teach or suggest water soluble derivatives of chitosan as examples of covalently crosslinkable polymers. Because Langer et al. is not directed to a semi-interpenetrating network in which hyaluronic acid or other anionic

polysaccharide is not crosslinked, there would be no motivation to alter the acetylation content of chitosan in order to obtain a derivative having the claimed acetylation content that is soluble at the claimed pH range. The crosslinking reaction of chitosan itself could simply be conducted in an acidic aqueous solution.

Based on the arguments presented above, the Examiner has failed to establish that the claimed invention would be obvious in view of Langer et al. and further in view of Hudson et al. Withdrawal of this rejection is therefore respectfully requested.

A general authorization is hereby granted to charge Deposit Account No. 502807 for any fees required under § 37 C.F.R. 1.16 and 1.17 in order to maintain pendency of this application.

Conclusion

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 251-3509.

Respectfully submitted,

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